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Review Article

Endomyocardial biopsy in patients with acute myocarditis, idiopathic dilated cardiomyopathy, and arrhythmogenic right ventricular dysplasia

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Abstract: Endomyocardial biopsy (EMB) is useful for the diagnosis of myocarditis, cardiac sarcoidosis, and non-ischemic cardiomyopathy. In this mini-review, we discuss the diagnostic potential of EMB in cases of acute/chronic-active myocarditis, sarcoidosis, idiopathic dilated cardiomyopathy and arrhythmogenic right ventricular dysplasia. We also summarize the complications caused by endomyocardial biopsy procedures. Importantly, we finally review the emerging molecular biology technologies as well as biological engineering techniques that can help improve the diagnostic accuracy of EMB to diagnose myocarditis and cardiomyopathies, promoting the management of these diseases.

Keywords: Endomyocardial biopsy, acute myocarditis, idiopathic dilated cardiomyopathy and arrhythmogenic right ventricular dysplasia, complications

Introduction

Endomyocardial biopsy (EMB) is useful to establish a definite diagnosis of myocarditis, cardiac sarcoidosis, and non-ischemic cardiomyopathies [1-3]. The clinical and physiopathological relevance of biopsy-based diagnosis of myocarditis, cardiac sarcoidosis, and unexplained cardiomyopathies has been highlighted by several reports demonstrating the potential of EMB-based causal treatment strategies (immunosuppressive or antiviral therapies) and the advantage of EMB-based exploration of the etiology of cardiomyopathies. This is especially true when using EMB in combination with emerging molecular biology technologies, biological engineering techniques, and imaging tools such as cardiac magnetic resonance tomography (CMR) and positron emission tomography (PET) which can significantly improve the diagnostic accuracy for myocarditis, cardiac sarcoidosis, cardiomyopathies, or other diseases [4-10].

Because EMB is an invasive strategy with a potential risk of complications such as cardiac tamponade/pericardial effusion, pericardiocentesis, ventricular arrhythmias or complete atrioventricular block, its clinical use should only be practiced by experienced interventionalists who are following a strict protocol. This protocol includes several echocardiographic examinations before, immediately after, and one hour later to detect relevant hemopericardium that can be treated by regular pericardiocentesis. In case of continuous bleeding, a catheter can be left in place until the bleeding stops, which can sometimes be achieved even after two to three days. In the most severe situation, connection of the catheter inside the pericardial space to a mechanical autotransfusion system (e.g. Cell Saver®) or even electric pump can reinject the blood in the patient´s circulation. With these techniques, continuing tamponade requiring surgical intervention has been very rare.

EMB in acute myocarditis

In acute myocarditis, EMB is indicated when classical clinical signs associated with a significant decrease of LVEF with or without arrhyth-

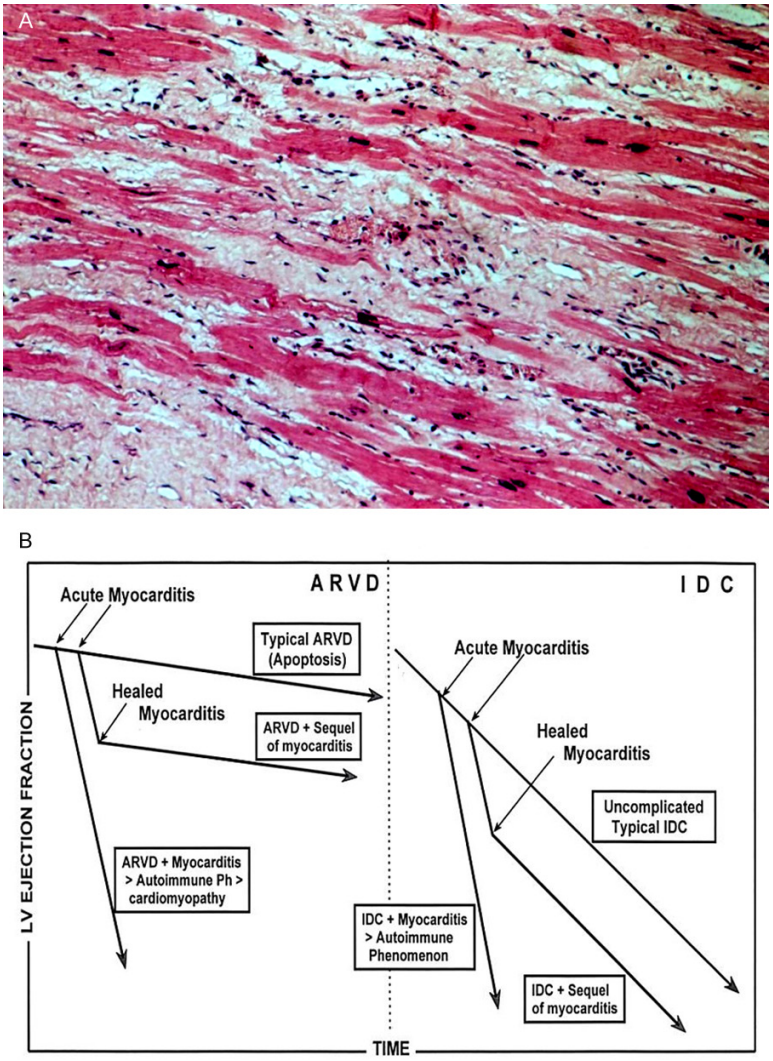

Figure 1. A: A 28-year-old male patient in whom the clinical course was illustrated by release of troponin and progressive decrease in left ventricular ejection fraction (LVEF), and finally heart transplant confirming the diagnosis of ARVD, but also showing a typical involvement of both ventricles by histological signs of lymphocytic myocarditis. A zone of chronic-active myocarditis in the LV in the same case indicated major loss of cardiac function leading to progressive deterioration of heart function and transplantation. (With permission from Ardan Saguner [12]). B: Role of superimposed myocarditis on deterioration of LVEF during follow-up in patients with ARVD and IDCM. This explains the wide spectrum of clinical evolution of heart failure well known in IDCM (With permission from Guy Fontaine [27]).

mias occur within 48 hours after the time of hospitalization [1, 3, 9, 11] because superimposed myocarditis in some patients with cardiomyopathies can lead to rapid disease progression eventually necessitating cardiac replacement therapy (**Figure 1**) [12, 13]. In such case, therefore, an early EMB is indicated and allows one to characterize and quantitate the presence of an inflammatory infiltrate with or without cardiomyocyte necrosis using classical histological and immunohistological techniques [1, 4, 11]. Moreover, available molecular techniques can allow a rapid simultaneous and reliable detection of cardiotropic viruses in EMB samples. This allows distinction of an auto-immune from a viral myocarditis, and therefore avoids the use of corticosteroids and immunosuppressive drugs in cases of ongoing viral cardiac infection [4]. When myocarditis is present, both ventricles can be affected in the same way. Therefore, EMB can be performed either on the right or the left ventricle free wall as well as in the right or left wall of the septum. Because of the well-known multifocal nature of myocarditis, 7-9 biopsy samples should be performed in both ventricles if the first biopsy taken from the right-sided septum is negative. Cerebral protection devices during left-sided biopsy can help to prevent procedure-related TIA/stroke (e.g. TriGUARD3™). In virologically well-identified infectious myocarditis preventing direct viral damage using specific antiviral therapy becomes one possible approach in clinical trials or in temporary authorized use of drugs [1, 4, 9, 14].

EMB in idiopathic dilated cardiomyopathy

In idiopathic dilated cardiomyopathy (IDCM), EMB is indicated in cases of acute symptoms of heart failure refractory to traditional strategies [4, 14, 15]. Histological and immunohistological examination of EMB tissue allows to confirm the clinical and imaging based diagnosis by the detection of interstitial fibrosis associated with the absence of inflammatory infiltrates, allowing to rule out an acute or a chronic-active form of myocarditis [8]. Various common viral genomes could be amplified in EMBs from IDCM patients.

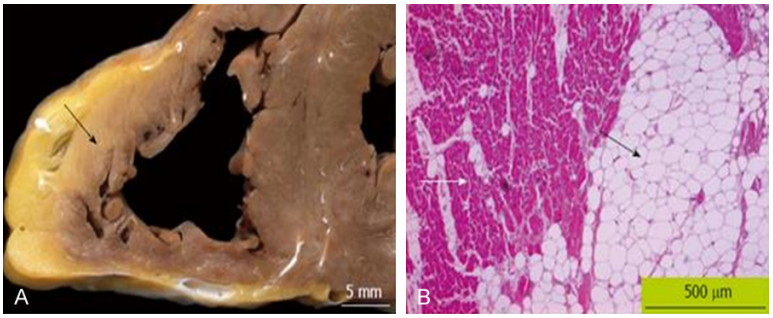

Figure 2. Typical pathology findings in arrhythmogenic ventricular cardiomyopathy/dysplasia (ARVC/D). A: Macroscopic finding in a patient with arrhythmogenic right ventricular cardiomyopathy/dysplasia. The myocardium of the right ventricular free wall is partially replaced by fibro-fatty tissue (black arrow) that typically begins in the epicardial region and at later stages expands transmurally; B: Endomyocardial biopsy from a patient with ARVC/D demonstrating fatty (black arrow) replacement of the right ventricular myocardium. Strands of myocardium are still visible (White arrow, heidenhain trichrome, magnification × 60). (With permission from Ardan Saguner [23]).

The presence of two or even three viruses in the same patient are markers of poor outcome [15, 16]. Cardiac viral infections could trigger or contribute as co-factors to the development of the disease in a large fraction of IDCM patients. Some viral infections in IDCM patients could predict a bad long-term prognosis. Altogether this evidence supports the concept of the existence of a subset of viral-infection based DCM among IDCM patients [1]. In IDCM patients, the molecular identification of viral cardiotropic agents and the assessment of viral load levels could be of major interest to establish a prognostic marker of heart failure evolution, and therefore to improve monitoring and therapeutic management. Currently, the progress of molecular biology leads to rapid and accurate viral detection in EMB, especially in patients admitted to the hospital due to unexplained heart failure such as individuals with IDCM. Practically, these emerging biotechnologies have positive effects in promoting the management of patients with IDCM, but also to evaluate the impact of common human cardiotropic viruses such as enteroviruses, HHV6 and parvovirus B19 in DCM [5, 7, 8, 10]. Notably, in some cases of IDCM, there can also be the completely healed form where one sees hyaline fibrosis with no lymphocytes.

EMB in arrhythmogenic right ventricular dysplasia

Arrhythmogenic right ventricular dysplasia (ARVD) was recognized in 1977 during antiarrhythmic surgery in Pitié Salpêtrière Hospital (Paris, France) [17]. The dysplasia predominantly involved the original right ventricular "triangle of dysplasia". The diagnosis of ARVD was pathologically based on our previous findings of myocardium embedded in or bordered by fatty tissue and/or fibrosis (**Figure 2**) [17, 18]. Biventricular involvement is very frequently observed at later stages (**Figure 3A**); surviving cardiomyocytes (**Figure 3B**) and zones of fibrosis (**Figure 3C**) are observed in the same patient on the right as well as external part of the left ventricle, leading to congestive heart failure and death [14, 19-23]. In ARVD cases, EMB is not routinely indicated because the diagnosis is based on the association of arrhythmias, specific ECG features, cardiac echocardiographic abnormalities, cardiac magnetic resonance imaging, RV angiography, and family history and genetic testing [21]. The severe progression in ARVD could be also the result of co-factors related to the environment as common cardiotropic viruses or bacteria. Some published cases have demonstrated in ARVD patients the presence of an active myocarditis "superimposed" on the genetic background of ARVD [12, 13, 24, 25]. This phenomenon of a superimposed inflammatory process can explain the wide spectrum of disease progression in ARVD, which could be related to the susceptibility of the patient for a particular virus and the kind of virus involved in this co-factor of morbidity. Further prospective clinical studies on ARVD should include EMB sampling to explore the pathophysiological mechanisms and more specifically the presence of myocardial infection by common cardiotropic viruses. In order to secure EMB sampling and to exclude patients with a potentially increased risk of perforation during EMB, CMR, PET or 3D electroanatomical voltage mapping can be used to localize the substrate in order to increase the diagnostic yield, and also to avoid EMB from unaffected regions or thin fibro-fatty areas in the RV myocardium that are particularly prone to perforation.

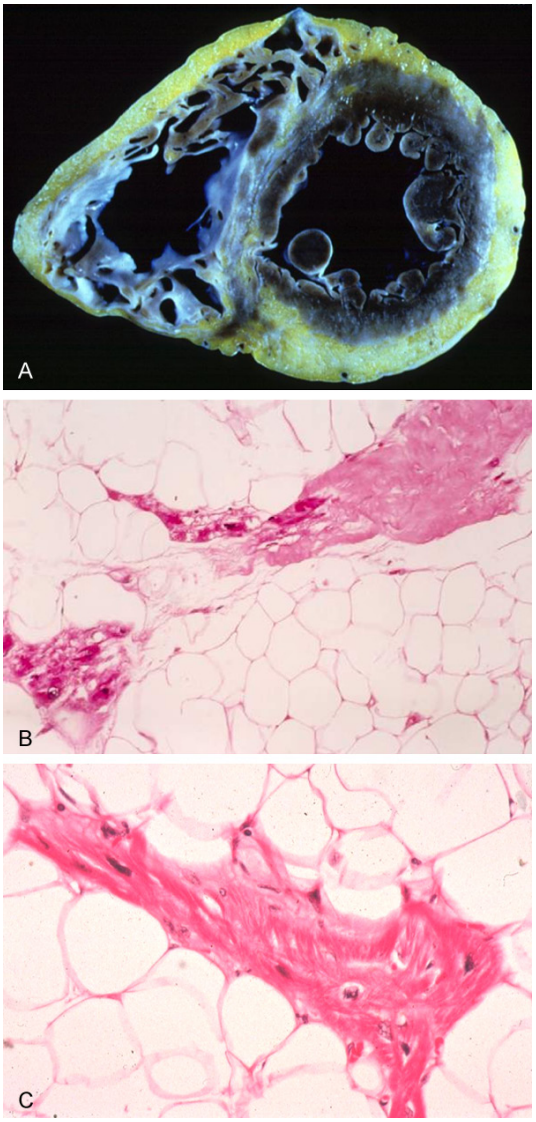

Figure 3. Representative biventricular dysplasia in ARVD. Biventricular dysplasia. The same disease process, replacement of myocardium by fat and fibrosis, is observed in this patient on the right as well as the external part of the left ventricle (A). Inside fat, there are surviving cardiomyocytes (B) and zones of fibrosis (C). (With permission from Guy Fontaine [22]).

Conclusions

EMB is still regarded as the gold standard to establish the diagnosis of some cardiovascular diseases, which are difficult to diagnose by noninvasive testing. Moreover, histopathological, immunological and virological information provided by analyses of EMB samples are of major interest to evaluate present or future causal treatment strategies (immunosuppressive or antiviral therapies), and to explore the pathophysiological mechanisms of etiologically unknown cardiomyopathies [15, 16, 26]. The new reliable and safe CMR and PET scan protocols used in the diagnosis of myocarditis, cardiac sarcoidosis, or unexplained cardiomyopathies remain to be prospectively validated against classical EMB procedures, allowing the characterization of myocardial lesions and inflammatory processes induced directly by exogenous factors (toxins, drugs, viruses, bacteria, parasites) or indirectly by autoimmune mechanisms.

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Disclosure of conflict of interest

None.

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